

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

32-254P

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)

09/530013

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PRIORITY DATE CLAIMED

PCT/JP98/01470

March 31, 1998

October 24, 1997

TITLE OF INVENTION

METHOD FOR INHIBITING DECOMPOSITION OF NATRIURETIC PEPTIDES AND IMPROVED METHOD FOR ASSAYING
NATRIURETIC PEPTIDES WITH THE USED OF THE SAME

APPLICANT(S) FOR DO/EO/US

SHIMIZU, Hiroyuki; ASADA, Hidehisa; ENDO, Kazuaki

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

- ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
- a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
- b. ☒ has been transmitted by the International Bureau.
- c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(3)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(2)).
- a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
- b. ☐ have been transmitted by the International Bureau.
- c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
- d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.-1449 and International Search Report (PCT/ISA/210)
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
1.) Three (3) sheets of Formal Drawings

09/530013

PCT/JP98/01470

17 ☒ The following fees are submitted:**BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):**

Neither international preliminary examination fee (37 CFR 1.482)
nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO
and "International Search Report not prepared by the EPO or JPO" \$970.00

International preliminary examination fee (37 CFR 1.482) not paid to
USPTO but International Search Report prepared by the EPO or JPO \$840.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO
but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$690.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO
but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$670.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO
and all claims satisfied provisions of PCT Article 33(1)-(4) \$96.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30
months from the earliest claimed priority date (37 CFR 1.492(e)).

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total Claims	11 - 20 =	0	X \$18.00
Independent Claims	2 - 3 =	0	X \$78.00

MULTIPLE DEPENDENT CLAIM(S) (if applicable) Yes + \$260.00

TOTAL OF ABOVE CALCULATIONS =

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity statement
must also be filed (Note 37 CFR 1.9, 1.27, 1.28).

SUBTOTAL =

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☐ 30
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TOTAL NATIONAL FEE =

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be
accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +

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Amount to be:
refunded \$
charged \$

a. ☒ A check in the amount of \$ 1140.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of \$ _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any
overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:

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SIGNATURE

STEWART RAYMOND C.
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REGISTRATION NUMBER

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: SHIMIZU, Hiroyuki et al.
Int'l. Appl. No.: PCT/JP98/01470
Appl. No.: New Group:
Filed: April 24, 2000 Examiner:
For: METHOD FOR INHIBITING DECOMPOSITION
OF NATRIURETIC PEPTIDES AND
IMPROVED METHOD FOR ASSAYING
NATRIURETIC PEPTIDES WITH THE USE
OF THE SAME

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION

Assistant Commissioner for Patents
Washington, DC 20231

April 24, 2000

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/JP98/01470 which has an International filing date of March 31, 1998, which designated the United States of America.--

IN THE CLAIMS:

Please amend the claims as follows:

Claim 4: Line 1, change "any one of claims 1 to 3" to --
claim 1 or 2--

Claim 5: Line 1, change "any one of claims 1 to 4" to --
claim 1 or 2--

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 
Raymond C. Stewart, #21,066

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416 Rec'd PCT/PTO 24 APR 2000

DESCRIPTION

METHOD FOR INHIBITING DEGRADATION OF NATRIURETIC PEPTIDES AND IMPROVEDMETHOD FOR MEASURING NATRIURETIC PEPTIDES WITH THE USE OF THE SAME

Technical Field

This invention relates to methods for inhibiting the degradation of natriuretic peptides by using a container which comprises a material inhibiting the activation of a substance degrading the peptides and also relates to methods for measuring, assaying, collecting, and storing of the peptides by using the container.

Background Art

A natriuretic peptide family consists of at least three types of natriuretic peptides, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C type natriuretic peptide (CNP). CNP is a vascular proliferation-regulating peptide mainly secreted from endothelial cells. ANP and BNP are cardiac hormones mainly synthesized in and secreted from heart. These peptides are synthesized as pro-hormones and cleaved to be mature peptides, α -ANP, α -BNP, α -CNP respectively. Human α -ANP, α -BNP, and α -CNP consist of 28, 32, and 22 amino acid residues, respectively.

Some diseases cause the secretion of these natriuretic peptides into blood stream. Since the synthesis and secretion of ANP and BNP are promoted mainly by a load against atria and ventricles of heart, respectively, their secretions reflect changes of heart functions. Each peptide is used as a diagnostic indicator of heart diseases, especially heart failure. Measurement of both α -ANP and α -BNP by immunoassay has already been applied in the clinical field.

Since α -ANP and α -BNP are easily degraded by proteases in blood after

the collection, they are extremely unstable in blood samples. Thus results of measurement had been greatly affected by the collecting methods, storing methods of specimens and the period from collection to measurement. To measure the concentration of the peptides exactly, addition of degradation inhibiting agents, e.g., aprotinin etc. or keeping specimens at low temperature had been essential. But, these handlings were complicate, required too many tasks, and not completed methods as pretreatment of specimens.

Disclosure of Invention

It is speculated that after blood collection natriuretic peptides are degraded by substances such as proteases in blood. To date, some protease inhibitors were added into the samples for the inhibition of the degradation of natriuretic peptides. But, it could not completely inhibit the degradation. The present inventors have speculated that coagulation factors activated by negatively charged solid phase such as glass surface accelerate the degradation of natriuretic peptides when specimens are collected into a container made of glass. The inventors have collected specimens by using a glass container wherein the face coming into contact with a specimens was coated with silicon, and obtained a result that the degradation of natriuretic peptides were inhibited.

The inventors have found out that the degradation of natriuretic peptides by a substance such as proteases can be suppressed significantly by using a container coated with silicone upon measurement of natriuretic peptide.

The inventors have also found out that the degradation of natriuretic peptides can be suppressed by using a container made of plastic such as polyethylene terephthalate (PET), polystyrene, polypropylene, polyethylene

and acrylic resin.

These results suggest that the degradation of natriuretic peptides in specimens can be suppressed by using a container wherein the face coming into contact with specimens is made of a material inhibiting the activation of a substance degrading the peptides upon handling specimens containing mammalian natriuretic peptides. Therefore, it is expected that the former complicated handling of specimens can be eliminated by using a container wherein the face coming into contact with specimens is made of materials other than glass upon the measurement of natriuretic peptides. Further expected is that these convenient specimens collecting methods for sample preparation give more exact results for diagnosis of heart diseases than conventional methods already used in the clinical field.

This invention is based on the results of the measurement of natriuretic peptides by thus established methods for the inhibition of degradation of mammalian natriuretic peptides by using a container which do not activate substances degrading the peptides in handling specimens containing the peptides.

This invention relates to a method for inhibiting the degradation of mammalian natriuretic peptides by using a container wherein the face coming into contact with specimens made of a materials, preferably, silicone or plastic, which inhibits the activation of the substances degrading the peptides.

Mammalian natriuretic peptides comprise at least ANP and BNP and precursors and derivatives of each peptide because in body there are not only the mature types but also the precursors such as γ -ANP and γ -BNP (BBRC, 214(3), (1995)), and their derivatives. Mammal means all kinds of mammal having natriuretic peptides, such as human, dog, pig, rat and mouse.

"Handling of specimens" means any kinds of handling for specimens, such

as collection, storage, analysis, measurement and so on of the specimens.

"Materials inhibiting the activation of a substance degrading peptides" mean materials, which can inhibit the activation of substances degrading the peptides, such as proteases etc., and can at least form the face coming into contact with the specimen contained in a specimen collecting container. Examples of the material include silicone and plastic, preferably polyethylene, polyethylene terephthalate, polystyrene, polypropylene, polyamide, acrylic resin and so on. SILICONIZE L-25 (Ficon Co.) is given for example as commercially available silicone. It is possible for persons skilled in the art to coat usually used containers made of glass and polyethylene with silicone by using this reagent.

"Container" means all kinds of containers for specimen collection, storage, measurement and so on, for example, a container which is made of or coated with a material inhibiting the degradation, preferably, with silicone or plastic.

Any kind of biological samples can be used for measuring specimens, and preferred is whole blood or blood plasma.

This invention relates to a measurement of natriuretic peptide in specimens which do not contain aprotinin.

Although aprotinin has been added into specimens to inhibit the degradation of natriuretic peptides by proteases which are already active in blood or are activated after blood collection, it can not inactivate them contained in biological samples completely.

This invention relates to a measuring method of mammalian natriuretic peptides which comprises the method for inhibiting the degradation of the peptides.

The measurement of natriuretic peptides can be carried out by a biological activity measurement, liquid chromatography, immunoassay and so

on. The immunoassay can be performed, which may be competitive immunoassay or sandwich immunoassay, by persons skilled in the art. Otherwise, commercially available α -ANP assay kit "SHIONORIA ANP" (Shionogi & Co., Ltd.) or α -BNP assay kit "SHIONORIA BNP" (Shionogi & Co., Ltd.) can also be used for the measurement.

Furthermore, this invention relates to a kit for measuring mammalian natriuretic peptides. The kit comprises the method for inhibiting the degradation of the peptides in a specimen by using a container wherein the face coming into contact with the specimen is made of a material inhibiting the activation of a substance degrading the peptides upon the specimen collection or measurement.

Brief Description of Drawings

Fig. 1 shows the relationship between the storing periods in glass tubes or silicone-coated glass tubes at 25°C and the residual activities of BNP like substances measured by various kinds of BNP measuring methods.

Fig. 2 shows the relationship between the storing periods in silicone-coated or non-coated polyethylene terephthalate tubes or glass tubes at 25°C and the residual activities of BNP like substances.

Fig. 3 shows the residual BNP activities of BNP like substances stored in silicone-coated or non-coated glass tube and various kinds of plastic tubes, such as polystyrene, polypropylene, reinforced polyethylene and acrylic resin for 24 hours at 25°C.

Example

More detail of this invention is explained in the following examples, which does not limit this invention.

Example 1

Measurement of BNP using glass tubes

(1) Preparation of silicone coated glass tubes: Commercially available glass tubes (Terumo, Tokyo, Japan) were washed with purified water once, and with 3% (V/V) silicone solution (SILICONIZE L-25; Ficon Co.,) three times. They were washed once again with purified water and dried for 90 min at 300 °C

(2) Preparation of a specimen for measurement: Venous blood from normal subject was collected into a blood-collecting tube containing EDTA (1.5 mg/ml EDTA·2Na). Human α -BNP (Peptide Institute, Osaka, Japan) was added to the collected blood to make its final concentration 200 pg/ml, to prepare a specimen.

(3) BNP measurement by IRMA method: The specimen was pipetted into the silicone-coated tubes and the non-coated tubes, respectively. They were allowed to stand for 0, 2, 6, and 24 hours at room temperature (25 °C). Blood cells were separated from these specimens by a centrifugation (Kokusan: H-107GA), $\times 2000$ g, for 5 min at 4°C. These specimens were stored at - 80 °C. BNP immunoreactivities were measured by SHIONORIA BNP (Shionogi).

Briefly, 100 μ l of plasma or standard solution (α -BNP solutions: 0, 4, 10, 150, 600, and 2000 pg/ml), were pipetted into Shionogi tubes (made of polystyrene: Shionogi), respectively. Two hundreds μ l of iodine labeled anti-BNP antibody solution and a anti-BNP antibody immobilized polystyrene bead were added into the tubes. The mixture was stirred and then left alone for 18 hours at 4°C. After washing twice with 2 ml of washing solution, the radioactivities were measured by γ -counter ARC-600 (Aloka). The result is shown in Fig.1.

In the case of using non-coated glass tubes (Figure 1, ■), the ratio of residual BNP activity was about 20 % after 24 hours-standing. On the other hand, the residual BNP activity ratio was about 80 % even after 24 hours-standing and the activity of substances degrading peptides was suppressed by using the silicone-coated glass tubes (Fig.1, □)..

Fig.1 shows that the activity of substances degrading natriuretic peptides can be suppressed by silicone-coating the face coming into contact with the specimen in a specimen collecting container.

Example 2

Measurement of BNP using polyethylene terephthalate(PET) tubes

- (1) Preparation of silicon-coated PET tubes: Commercially available PET tubes (Terumo, Tokyo, Japan) were washed with purified water once, and with 3 % (V/V) silicone solution (SILICONIZE L-25: Ficon Co.) three times. They were washed once again with purified water and dried.
- (2) Preparation of a specimen for measurement: Fifty ml of venous blood from normal subject was collected into a blood-collecting tubes containing EDTA (1.5 mg/ml EDTA-2Na). Human α -BNP (Peptide Institute) was added to the collected blood to make its final concentration 200 pg/ml, to prepare a specimen.
- (3) BNP measurement by IRMA method: The specimen was pipetted into the silicone-coated PET tubes, the silicone-coated glass tubes, the non-coated PET tubes and the non-coated glass tubes, respectively. They were allowed to stand for 0, 2, 6, 24, and 72 hours at room temperature (25 °C). Blood cells were separated from these specimens by a centrifugation (Kokusan: H-107GA), $\times 2000$ g, for 5 min at 4°C. These specimens were stored at - 80 °C. BNP immunoreactivities in these blood plasma were measured by SHIONORIA

BNP (Shionogi). The measurement was performed by the same method as that described in Example 1.

The result is shown in Fig.2. The ratio of residual BNP activity was about 80% after 24 hours-standing due to the suppression of the activity of substances degrading peptides by using the silicone-coated PET tubes (Fig.2, ○) and the non-coated PET tubes (Fig.2, ●). The result was the same as that of using the silicone-coated glass tubes (Fig.2, □). On the other hand, the ratio of residual BNP activity was 0 % after 24 hours-standing by using the non silicone-coated glass tubes (Fig.2, ■).

Example 3

Measurement of BNP using plastic tubes

As specimen storing containers, glass tubes, silicon coated glass tubes, and plastic tubes were used. Five kinds of plastic tubes, i.e., polystyrene tubes, polypropylene A tubes, polypropylene B tubes, reinforced polyethylene tubes, and acrylic resin tubes were used.

(1) BNP measurement by IRMA method

The specimen was pipetteed into each of the above described plastic tubes, coated with or without silicone. They were allowed to stand for 0, and 24 hours at room temperature (25 °C). Blood cells were separated from these specimens by a centrifugation (Kokusan: H-107GA), $\times 2000$ g, for 5 min at 4 °C. The obtained plasma specimens were stored at - 80 °C. BNP immunoreactivities in these plasma specimens were measured by SHIONORIA BNP (Shionogi). The measurement was performed by the same method as Example 1.

The ratios of the residual BNP activities were 50% or more due to the suppression of the activity of substances degrading peptides by using any kinds of plastic tube used, i.e., polystyrene tube, polypropylene A tube,

polypropylene B tube, reinforced polyethylene tube, and acrylic resin tube (Figure 3, lane 3, 4, 5, 6, and 7). The result was the same as that by using the silicone-coated glass tube (Figure 3, lane 2). On the other hand, the ratio of residual BNP activity was 0 % by using the non-coated glass tube (Fig. 3, lane 1).

The residual activity of BNP remarkably decreased in glass tubes because BNP was degraded by substances degrading the peptides such as proteases. While the decrease of the residual BNP activity was suppressed in silicon-coated glass tubes. Furthermore, in plastic tubes made of polyethylene terephthalate, polystyrene, polypropylene, polyethylene or acrylic resin coated with or without silicone, the degradation of BNP was suppressed due to the inhibition of the activation of substances degrading peptides.

Effect of Invention

The method of this invention for inhibiting the peptide degradation by using a container wherein the face coming into contact with a specimen is made of a materials inhibiting the activation of the degrading substances, provides stable and dependable clinical data on which collecting methods, storing methods and period till measurement do not have any effects.

Further, it will contribute to an exact diagnosis of heart disease by providing economical, convenient stable and dependable clinical data because blood samples can be used for measuring without complicate handling.

CLAIMS

1. (Amended) A method for inhibiting the degradation of mammalian natriuretic peptides in specimen, which comprises using, upon handling the specimen, a container wherein the face coming into contact with the specimen is made of or coated with a material inhibiting the activation of a substance degrading the peptides.
2. The method as claimed in claim 1, wherein said material is silicone or plastic.
3. The method as claimed in claim 1 or 2, wherein said mammal is human, dog, pig, rat and mouse.
4. The method as claimed in any one of claims 1 to 3, wherein said natriuretic peptide is BNP.
5. The method as claimed in any one of claims 1 to 4, wherein said specimen does not contain aprotinin.
6. A method for measuring mammalian natriuretic peptides, which comprises the method as claimed in claim 1.
7. (Amended) A kit for measuring mammalian natriuretic peptides, which comprises a container wherein the face coming into contact with specimen is made of or coated with a material inhibiting the activation of a substance degrading the peptides.
8. The kit as claimed in claim 7, wherein said specimen does not contain aprotinin.

ABSTRACT

A method for inhibiting the degradation of mammalian natriuretic peptides, in particular, BNP by using containers wherein the face coming into contact with specimens are made of a material capable of inhibiting the activation of a substance degrading peptides. This method makes it possible to collect specimens for measuring natriuretic peptides stably and conveniently .

Also provided is a method for measuring natriuretic peptides by using these containers.

Figure 1

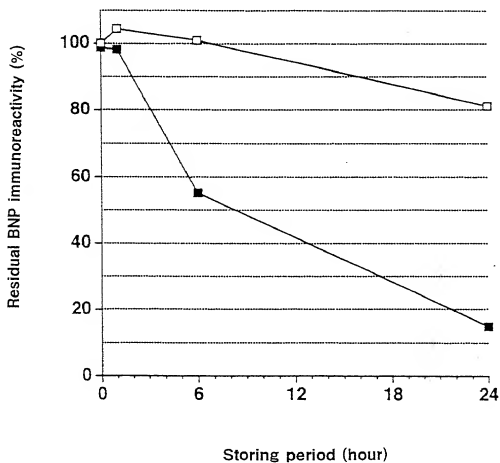


Figure 2

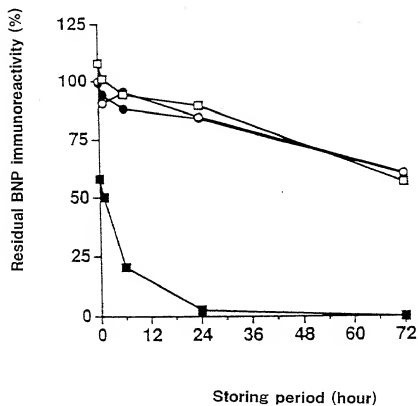
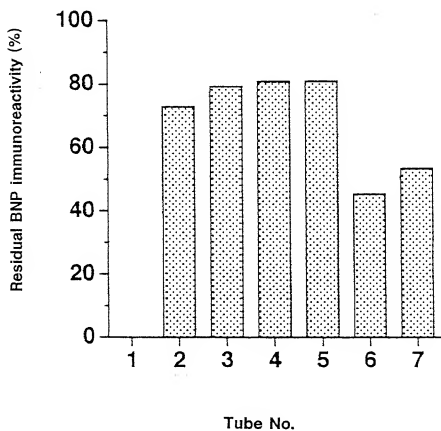


Figure 3



BIRCH, STEWART, KOLASCH & BIRCH, LLP

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ATTORNEY DOCKET NO.
32-254P

PLEASE NOTE:
YOU MUST
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FOLLOWING:

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if several inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title: →

METHOD FOR INHIBITING DEGRADATION OF NATRIURETIC PEPTIDES AND IMPROVED

METHOD FOR MEASURING NATRIURETIC PEPTIDES WITH THE USE OF THE SAME

Fill in Appropriate
Information —
For Use
Without
Specification
Attached: →

the specification of which is attached hereto. If not attached hereto,

the specification was filed on _____ as
United States Application Number _____
and amended on _____ (if applicable); and/or
the specification was filed on March 31, 1998 as PCT
International Application Number PCT/JP98/01470 _____; and was
amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

Insert Priority
Information: →
(if appropriate)

292982/1997

Japan

10/24/1997

(Number)

(Country)

(Month / Day / Year Filed)

☒ Yes ☐ No
☐ Yes ☐ No
☐ Yes ☐ No
☐ Yes ☐ No

(Number)

(Country)

(Month / Day / Year Filed)

(Number)

(Country)

(Month / Day / Year Filed)

(Number)

(Country)

(Month / Day / Year Filed)

Insert Provisional
Application(s): →
(if any)

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

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Application Number

Date of Filing (Month / Day / Year)

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(if appropriate)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States and/or PCT application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States and/or PCT application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Insert Prior U.S.
Application(s): →
(if any)

(Application Number)

(Filing Date)

(Status — patented, pending, abandoned)

(Application Number)

(Filing Date)

(Status — patented, pending, abandoned)

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

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Insert Name of
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Inventor, if any:
see above

Full Name of Third
Inventor, if any:
see above

Full Name of Fourth
Inventor, if any:
see above

Full Name of Fifth
Inventor, if any:
see above

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

GIVEN NAME <u>Hirayuki</u>	FAMILY NAME <u>SHIMIZU</u>	INVENTOR'S SIGNATURE <u>J. Shimizu</u>	DATE* <u>18 Feb. 2000</u>
Residence (City, State & Country) <u>Settsu-shi, Osaka-fu, Japan</u>		CITIZENSHIP <u>Japan</u>	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country) <u>c/o Shionogi & Co., Ltd. 5-1, Mishima 2-chome, Settsu-shi Osaka 566-0022 JAPAN</u>			
GIVEN NAME <u>Hidehisa</u>	FAMILY NAME <u>ASADA</u>	INVENTOR'S SIGNATURE <u>Hidehisa Asada</u>	DATE* <u>23 Feb. 2000</u>
Residence (City, State & Country) <u>Settsu-shi, Osaka-fu, Japan</u>		CITIZENSHIP <u>Japan</u>	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country) <u>c/o Shionogi & Co., Ltd. 5-1, Mishima 2-chome, Settsu-shi Osaka 566-0022 JAPAN</u>			
GIVEN NAME <u>Kazuaki</u>	FAMILY NAME <u>ENDO</u>	INVENTOR'S SIGNATURE <u>Kazuaki Endo</u>	DATE* <u>24 Feb. 2000</u>
Residence (City, State & Country) <u>Osaka-shi, Osaka-fu, Japan</u>		CITIZENSHIP <u>Japan</u>	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country) <u>c/o Shionogi & Co., Ltd. 12-4, Sagisu 5-chome, Fukushima-ku Osaka-shi, Osaka 553-0002 JAPAN</u>			
GIVEN NAME	FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Residence (City, State & Country)		CITIZENSHIP	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)			
GIVEN NAME	FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
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